CNI621 5/99
CLINICAL NUTRITION INSIGHTS

Vol. 6, No. 21

Breakthrough Technology Produces Concentrated Whey Protein with Bioactive Immunoglobulins

By David O. Lucas, Ph.D.

ABSTRACT: *Whey protein is believed to be the highest quality protein available, even when compared to egg, casein, milk, beef, or soy. It contains all essential and non-essential amino acids and is an excellent source of glutamine and the branched-chain amino acids that are necessary for new cell growth. While whey protein supplements have been available for many years, a multi-patented, breakthrough process has been developed that produces a unique whey protein concentrate that contains high levels of naturally occurring, bioactive immunoglobulins. These immunoglobulins, or antibodies, promote the activity level of the immune system and are believed to support healthy, efficient intestinal function. For providing both a basic dietary form of high quality protein and for immune support, this concentrated whey protein is an excellent choice.*

Whey, the curd-free portion of milk, is composed of an array of high and low molecular weight constituents including proteins, carbohydrates, minerals, enzymes, and vitamins. The main protein fractions of whey are alpha-lactalbumin, beta-lactoglobulin, serum albumin, lactoferrin, lactoperoxidase, and bioactive immunoglobulins (antibodies). The amounts of these proteins in different whey products vary considerably according to the milk source, the treatment of the milk in processing, and how the whey is processed. Differences are especially noted in the amount of immunoglobulins and the activity of these antibodies in whey products. This reveals differences in the degree of protein denaturation associated with varying processing techniques.

Development of a Unique, Patented Process

Reflecting breakthroughs in processing technology, a high quality whey protein concentrate (WPC) has been developed that contains 80% protein with all of the naturally occurring constituents remaining largely undenatured. It is produced through a patented series of separations, ultrafiltration/diafiltration, and lyophilization, which increases the protein content of the whey to approximately 80% while fat is reduced to less than 10%. This method utilizes controlled temperatures and pH to prevent the protein from denaturing (becoming inactive) and yields a product with a low ash, fat, and lactose content.

The whey source of this unique WPC is from the milk of a cow herd in New Zealand, one of only two "pristine herds" worldwide. This herd is free from disease, hyperimmunization, genetic alteration, and pesticide contamination. The final product is supplied in powder form, for the preservation of nutrients and potency of the protein without added preservatives.

Advantages of High Quality Whey Protein Concentrate

Dietary proteins differ in quality and, as a result, differ in their capacity to provide amino acids for utilization in the body.[1-3] A dietary protein that contains all of the essential amino acids in sufficient quantity and ratio is called a complete protein (high quality). A dietary protein that has a ratio of amino acids different from that of the average body protein, or deficient in one or more of the essential amino acids, is called an incomplete protein and is obviously less valuable for nutrition than a complete protein. Determining the biologic value (BV) of a protein involves measuring nitrogen (N) intake from the dietary protein and N output in the feces and urine, since N is unique to protein molecules.[1] Thus, BV is the fraction of absorbed N retained and used by the body for growth or maintenance.

WPC contains all essential and non-essential amino acids, and thus is a complete protein. The main protein fractions of WPC are lactalbumin, lactoglobulin, serum albumin, lactoferrin, and immunoglobulins.[4] As can be seen in Table 1, lactalbumin, the main component of WPC, has the highest BV of any other protein, including whole egg.[4] For years, casein was considered the "gold standard" of protein quality; however, its BV is far below that of lactalbumin, as well as in other measurements of protein quality. For providing both a basic dietary form of protein and for supplementation, the high BV of WPC makes it an excellent choice. WPC can also be added to other foods to considerably increase the BV of the mixture.

Table 1. Biologic Value (BV) of Dietary Proteins[4]

Protein	Biologic Value
Lactalbumin (whey)	104
Egg	100
Cow's Milk	91
Beef	80
Fish	79
Casein	77
Soy	74
Potato	71
Rice	59
Wheat	54
Beans	49

Due to its superior protein quality, WPC appears ideally suited to improve body composition and have positive anabolic effects. In addition to its high BV, WPC is high in cysteine and glutamine. These amino acids are required for the synthesis of glutathione, a key free radical scavenger in the body. Glutamine is also the predominant amino acid in skeletal muscle and provides both a source of fuel and precursors for growth to the rapidly dividing cells of the intestinal lining.[5] It is also an important fuel for lymphocytes (white blood cells) and macrophages. Thus, glutamine has been hypothesized specifically to improve immune function and to maintain intestinal integrity and barrier function.[5]

Naturally Occurring, Bioactive Immunoglobulins Found in High Quality Whey Protein Concentrate

Mammals, including humans, obtain immunity against microorganisms and their toxins before or shortly after birth by the transfer of immunoglobulins from the maternal body to the newborn.[4] Immunoglobulins (Ig) are protein molecules that function as antibodies against many pathogenic as well as potentially pathogenic microorganisms, such as bacteria and viruses.[1] In man, these immune enhancing proteins, mainly IgG, pass from the maternal blood to the baby in the uterus so that the baby is born with a passive immunity. In the cow and in humans, Ig are transferred in high quantities after birth in the colostrum, or "mother's first milk," and in lower quantities thereafter.[4] These antibodies are found in WPC and are non-differential, meaning that antibodies derived from bovine sources are active against the same diseases in humans and other species.

The intestinal tract provides the first line of defense as an immune barrier to foreign antigens or organisms that pass through the intestinal lumen.[1] Therefore, intestinal immune function is especially crucial. Because digestive enzymes do not break down Ig, they enter the intestine intact where they not only play a role in the defense of the intestinal mucosa against invading organisms, but also prevent the absorption of foreign proteins. Immunoglobulins also work to increase the activity level of the immune system. Through these attributes, Ig make an important contribution to restoring the integrity of a damaged intestinal tract, so that valuable nutrients can once again be utilized.

The predominant Ig in WPC is IgG, which comprises about 75% of the antibodies of the normal person.[1,4] Other immune enhancing substances are found in WPC, such as lactoferrin, beta-lactoglobulin, and alpha-lactalbumin.[4] Lactoferrin plays an important role in the resistance against intestinal infections, particularly *Escherichia coli*.[6] Its bacteriostatic effect is thought to be due to its ability to bind iron and thus to inhibit the growth of bacteria which require iron. The digestion of lactalbumin also yields bactericidal substances that may inhibit the growth of organisms in the small intestine.[4]

Animal studies have shown that a WPC was found to be as effective as colostrum in protecting newborn calves from disease.[7] Furthermore, a lower level of the concentrated whey was required to provide this protection (27 grams of concentrated whey vs. 100 grams of colostrum). In addition, serum Ig levels of 1-3 mg/ml using the WPC provided the same benefit as 10 mg/ml serum Ig levels using colostrum.[7]

The Vital Roles of Protein

Proteins perform a major structural role not only in all body tissues but also in the formation of enzymes, hormones, and nucleoproteins.[1-3] In anabolic processes they furnish the amino acids required to build and maintain body tissues. The great variety of proteins helps explain the diversity of their functional roles. Certain proteins transport oxygen, while others facilitate muscle contraction. As antibodies, they are involved in the function of the immune system. As an energy source, proteins are equivalent to carbohydrates in providing 4 kcal per gram; however, protein is not metabolized for energy except as needed in the fasting state or during extended physical exertion. In the form of lipoproteins, they participate in the transportation of triglycerides, cholesterol, phospholipids, and fat-soluble vitamins. Many vitamins and minerals are bound to specific protein carriers for transport. Proteins also contribute to homeostasis by maintaining normal osmotic relations among body fluids. In other words, proteins play a vital role in virtually every metabolic, structural, and physiologic process required for life!

Protein Metabolism

The overall metabolism of protein in the body is summarized by nitrogen balance, which is the difference between N intake through dietary protein and N output in the urine and feces.[1,3] Turnover of protein encompasses synthesis (anabolism) and degradation (catabolism). When these are equal, body protein is held constant. Various hormones secreted by the endocrine glands can alter the balance between tissue proteins and circulating amino acids. Growth hormone and insulin increase the formation of tissue proteins (synthesis), and the adrenocortical glucocorticoid hormones increase the concentration of circulating amino acids (degradation).

Digestion of protein occurs mostly in the upper small intestine under the influence of the proteolytic enzymes secreted from the pancreas.[1-3] After intestinal absorption of the resulting amino acids and peptides, the liver monitors and adjusts the rate of their metabolism according to bodily needs. Amino acids are transported through cell membranes by facilitated or active transport utilizing carrier mechanisms. Almost immediately after entry into the cells, the amino acids are combined by peptide linkages to form cellular proteins. Many of these intracellular proteins can be rapidly decomposed again into amino acids and transported back out of the cell into the blood, maintaining a constant equilibrium between plasma amino acids, plasma proteins, and the tissue proteins. It has been estimated that about 400 grams of body protein are synthesized and degraded each day as part of the continual state of flux of amino acids.

Daily Protein Requirements

A daily protein requirement of 0.8 grams per kilogram (1 kg = 2.2 lb.) body weight has been established for adults in the U.S.[2] This amounts to 45 grams of protein per day for an adult female weighing 125 pounds, and 62 grams per day for an adult male weighing 170 pounds. In both adults and children, the body makes adjustments for low protein intake depending on the quality of the protein ingested and the level of energy intake.[1] Urinary nitrogen output falls drastically with low protein intake and after 4 or 5 days of negative nitrogen balance, equilibrium is reestablished at a lower level. Beyond a critical point,

however, the body can no longer adapt, and protein deficiency with edema, wasting of body tissues, fatty liver, dermatosis, diminished immune response, weakness, loss of vigor, and a host of other metabolic and physiologic consequences develop.

Except for the excess protein in the diet or the obligatory protein degradation each day, the body relies almost entirely on carbohydrates or fats for energy as long as these are available.[1] However, with individuals on low-carbohydrate reducing diets, or in cases of high-energy output, such as during intense training or endurance exercise, muscle protein is catabolized for energy. In extreme cases of starvation, when the quantity of stored fats begins to run out, the amino acids of the blood begin to be rapidly deaminated and oxidized for energy. From this point on, the proteins of the tissues degrade rapidly—as much as 125 grams daily—and the cellular functions deteriorate precipitously.

Application of High Quality Whey Protein Concentrate in Cachexic, Immune Compromised Individuals

A patented, WPC containing active immunoglobulins was developed for use as a protein supplement in cachexic, immune compromised individuals. Progressive inanition or wasting is a fundamental component of the complex phenomenon known as the anorexia/cachexia syndrome (ACS) of cancer or AIDS.[8] Wasting is defined as an involuntary loss of body weight, generally associated with reduced dietary intake. Cachexia is a complex diagnostic picture characterized by progressive nutritional deterioration and wasting.[9]

Clinical manifestations of cachexia routinely include anorexia, early satiety, weight loss, muscle atrophy, weakness, easy fatigue, impaired immune function, and a decline in motor and mental skills.[8,10] Progressive wasting may be related to an inability to meet nutritional intake requirements (impaired intake, digestion, or absorption) or abnormalities of metabolism, which include hypermetabolism (elevated resting energy expenditure) and hypercatabolism (elevated protein degradation). These metabolic abnormalities are believed to be driven to a large extent by inflammatory cytokines.[8,11,12]

HIV/AIDS—Cachexia and wasting occur as a result of human immunodeficiency virus (HIV) infection.[11,12] The Centers for Disease Control and Prevention (CDC) uses unintentional weight loss greater than 10% of usual weight in its definition of AIDS wasting.[13] In HIV-infected gay white men, weight losses of 10% or more have been associated with decreased survival, even after controlling for CD4 counts and other prognostic covariates. In a retrospective study of 2,382 HIV-infected adults, as little as a 5% weight loss over 4 months was associated with a significantly increased risk of opportunistic complications and death.[13]

Cachexia may occur soon after HIV infection, but the patient may maintain his weight until an opportunistic infection develops, causing anorexia and negative energy balance, which leads to wasting.[11] Because loss of muscle occurs during cachexia when weight loss may not be evident, by the time a patient comes to medical attention for wasting, muscle loss may be profound. This decline in muscle mass may be an important cause of the HIV-associated decreases in physical, metabolic, and immune functional status.[11]

The primary goals of nutritional therapy are the maintenance of normal nutritional indices and positive nitrogen balance and body weight. Because malnutrition may begin in asymptomatic stages of HIV infection, long before clinical signs and symptoms occur, early dietary interventions are important in the overall care and quality of life of patients with HIV. Interventions that can improve lean body mass, strength, and function are of great interest.

Cancer—Weight loss may become manifest early in the course of cancer, often as a presenting feature of the disease. It has been cited by many as a major prognostic indicator of poor survival as well as poor response to therapy.[9,10,14] The progressive nutritional deterioration so frequently encountered in cancer patients, referred to as cachexia, is a major cause of morbidity and mortality in the cancer population.[10,14] Diminished nutritional intake, maladaptive metabolic processes, and increased metabolic expenditure all play roles in the development of this syndrome.[10]

Because nutrition plays a significant role throughout the clinical course of the cancer disease process, early diagnosis and intervention of nutritional risk or deficit may well be the foundation of treatment. Prevention of progressive nutritional deterioration—maintenance of body composition and nutritional status rather than attempting repletion—is the optimal strategy.[9,12]

Clinical Trials with WPC Supplementation

Several unpublished clinical trials have been conducted using a patented WPC developed for use with immune-compromised, cachexic individuals.[15-17] In addition to being a source of high quality protein, this WPC contains many other naturally occurring constituents found in whey that remain largely undenatured and bioactive.

- In a trial of 20 healthy subjects, the WPC was shown to increase the body's CD4 count (a measurement of the immune system) by a mean value over baseline of 16% to 23% throughout the course of the 20-day study.[15]

- A nutritional study was conducted with 35 patients to study the effects of two different doses of WPC in reversing cachexia (wasting syndrome) in AIDS patients.[16] Patients were randomized to receive either 20 g of WPC daily or 60 g of WPC daily (20 g/3 times per day) mixed with cold food or beverage. Of the 29 patients who completed the 6-week study, 25 either maintained their body weight and body cell mass or experienced an increase in one of the two parameters. No significant difference was detected between the two doses. Nine patients complained of transient, mild to moderate gastrointestinal side effects; however, only one patient withdrew from the study as a result of side effects.

- Two concurrent clinical trials were conducted utilizing WPC in a total of 62 AIDS patients (n=46 and n=16) experiencing undesired weight loss (wasting) of 5 pounds or more in the previous 6 months.[17] Patients consumed 20 g of WPC in addition to their normal diet for 8 weeks. Over the 8-week period, a majority of the patients gained weight (59% in one group and 50% in the other) with an average gain of 5.3 lbs. and 9.7 lbs., respectively.

Clinical Applications of High Quality Whey Protein Concentrate

Numerous stresses to the body can greatly increase the body's protein requirement.[5] Some of these stresses include illness or disease, physical injury, surgical trauma, malnutrition, emotional stress, and vigorous exercise. Therefore, those who can benefit from a high quality protein supplement include HIV/AIDS patients, cancer patients (especially those undergoing chemotherapy), people with digestive diseases, anorexic patients, and pre- and post-operative patients.

While in most cases Americans consume adequate amounts of protein, a great deal of that protein is often derived from high-fat sources such as red meat. Because of the cardiovascular and other health risks associated with the consumption of animal fat, a high quality protein supplement that is low in fat is a healthier alternative. In addition, many individuals who have trouble meeting their protein needs can benefit from a high quality, convenient source of protein: children, the elderly, and athletes, as well as those who lead a busy lifestyle and find it difficult to eat a healthy, balanced diet.

Children—Infants and children have much greater protein requirements per unit of body weight than adults to meet the demands of physical growth and tissue maintenance.[2] Therefore, sources of protein should come from high BV foods. A deficient diet can put a child's development at risk. For instance, protein deficiency can lead to a reduced number of brain cells and a deficiency in essential amino acids impairs development.[4] The school-age child has increasing exposure to influences such as TV and peer pressure that greatly affect food choices and habits. Thus, parents may find it difficult to ensure that their children receive enough high quality protein in their diets. In addition, needs for protein are increased during periods of adolescent growth, especially during puberty in both sexes.

Elderly—With increasing age, skeletal muscle mass decreases and body fat mass increases.[2,11] Pound for pound, muscle tissue burns far more calories at rest than fat mass. Therefore, the age-related decline in lean body mass contributes to a lower basal metabolic rate in the elderly. While less energy is needed, the requirement for dietary protein and essential amino acids, particularly lysine and methionine, is increased because the capacity for synthesizing body proteins and the rate of protein metabolism is reduced and there is a loss of muscle tissue.[4] Women tend to be more protein deficient than men and therefore start to lose lean muscle mass earlier than men.

The consumption of high quality protein after the age of 50 is thought to prevent many metabolic disorders of old age, particularly those of the liver.[4] The optimum amount of protein is thought to be 1.2-1.5 g/kg body weight per day. In addition to its role in energy metabolism, the decline in skeletal muscle mass may contribute to age-related reductions in bone density, insulin sensitivity, and aerobic capacity. Thus, increasing muscle mass and strength may be an important way to increase functional independence and decrease the prevalence of many age-associated chronic diseases.[11]

Vegetarians—Protein requirements in various vegetarian diets may be met by applying the principle of variety by combining complementary plant proteins (e.g., rice and beans) to achieve the necessary balance of amino acids. For those vegetarians that accept milk products (lactovegetarian), supplementing the diet with WPC is an excellent way to ensure that protein needs are met. For those who do not accept milk products (vegan), soy protein is an alternative.

REFERENCES

1. Guyton AC. Protein Metabolism. In: Textbook of Medical Physiology 8th ed. Philadelphia (PA): W.B. Saunders; 1991.
2. Mahan LK, Escott-Stump S. Proteins. In: Krause's Food, Nutrition, and Diet Therapy 9th ed. Philadelphia (PA): W.B. Saunders; 1996.
3. Crim MC, Munro HN. Proteins and Amino Acids. In: Shils ME, Olson JA, Shike M, eds. Modern Nutrition in Health and Disease vol. 1. 8th ed. Malvern (PA): Lea & Febiger; 1994.
4. Renner E. Milk Protein. In: Milk and Dairy Products in Human Nutrition. Munich: Volkswirtschaftlicher Verlag; 1983.
5. Matthews DE, Battezzati MD. Regulation of protein metabolism during stress. *Curr Opin Gen Surg* 1993:72-77.
6. Arnold RR, Brewer M, Gauthier JJ. Bactericidal activity of human lactoferrin: sensitivity of a variety of microorganisms. *Infect Imm* 1980;28(3):893-96.
7. Hartman RJ, Doherty TV, McCloskey MJ. Colostrx supplement protects against challenge with enterotoxigenic *E. coli* in neonatal dairy calves. *Agr Prac* 1991;12:41.
8. Ottery FD, Walsh D, Strawford A. Pharmacologic management of anorexia/cachexia. *Sem Oncol* 1998;25(2 Suppl 6):35-44.
9. Ottery FD. Supportive nutrition to prevent cachexia and improve quality of life. *Sem Oncol* 1995;22(2 Suppl 3):98-111.
10. Puccio M, Nathanson L. The cancer cachexia syndrome. *Sem Oncol* 1997;24(3):277-87.
11. Evans WJ, Roubenoff R, Shevitz A. Exercise and the treatment of wasting: aging and human immunodeficiency virus infection. *Sem Oncol* 1998;25(2 Suppl 6):112-22.
12. Mulligan K, Bloch AS. Energy expenditure and protein metabolism in human immunodeficiency virus infection and cancer cachexia. *Sem Oncol* 1998;25 (2 Suppl 6):82-91.
13. Muurahainen N, Mulligan K. Clinical trials update in human immunodeficiency virus wasting. *Sem Oncol* 1998;25(2 Suppl 6):104-11.
14. Tisdale MJ. Cancer cachexia: metabolic alterations and clinical manifestations. *Nutrition* 1997;13:1-7.
15. Moffat C. Investigation #IMC-94-002. Salt Lake Clinic, Salt Lake City, UT (1994).
16. Brosgart C, Romeyn M, Lucas D, et al. Effect of whey-based bovine immunoglobulin in patients with HIV wasting. East Bay AIDS Center, Berkeley, CA/St. Francis Memorial Hospital, San Francisco, CA (1996).
17. Lucas D, Beal J, Cardona L. Protein supplement promotes gain in lean mass in patients with HIV and moderate weight loss. Associates in Medical and Mental Health, Tulsa, OK/The Friedburg Clinic, Ft. Lauderdale, FL (1997).